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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

HITOO NISHINO, ET AL. : EXAMINER: G.S. KISHORE

SERIAL NO: 09/556,701 :

FILED: APRIL 24, 2000 : GROUP ART UNIT: 1615

FOR: PHARMACEUTICAL OR FOOD COMPOSITION FOR TREATMENT OR PREVENTION OF BRAIN EDEMA

REPLY BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

The invention claimed in the present application is a method for the *treatment* of brain edema, comprising administering an effective amount of a composition comprising melatonin to a subject having brain edema. Thus, the subject treated according to the claimed invention is actually afflicted with brain edema. According, the method claimed in the present application is not directed to *preventing* brain edema.

Regarding WO '555 the Examiner's opinion is that "since ischemia is the causative factor of brain edema, ... a composition, which is able to prevent ischemia, would be preventing [sic] the edema also". In other words, Examiner's opinion is that, by removing the causative factor of brain edema (ischemia in the case of WO '555), the brain edema would be prevented.

That is naturally true. Without a causative factor, a disease will be prevented. However, the invention claimed in the present application is not directed to the prevention of brain edema by interfering with a causative factor. In the present application, as shown in

Example 3, ischemia is given to rats to cause brain edema. Additionally, brain edema itself is a causative factor of brain edema because of the "forest fire"-like expansion of brain edema (see pages 2 and 3 of the specification).

When a causative factor of brain edema is not inhibited, the brain edema resulting from the causative factor requires treatment by some means. However, WO '555 is silent regarding any means for treating brain edema.

Although WO '555 discloses a method for reducing a specific injury (high foot-fault rate) caused by ischemia, WO '555 does not provide one skilled in the art any suggestion about the method for treating the brain edema caused by ischemia, especially in the particular case of brain edema.

Brain edema has a specific and characteristic feature, i.e., "forest fire" manner expansion (see pages 2 and 3 of the specification). Because of the specific feature of brain edema, one skilled in the art would expect that even when the initial fire (ischemia) could be extinguished (removed), the expanding forest fire (brain edema) could not be extinguished (treated). Firemen would need other means than extinguishing the initial fire, to prevent forest fire expansion (brain edema). The means that the inventors have found for preventing forest fire expansion (brain edema) is protection of astroglia (see the second paragraph at page 7 of the specification).

As described in the specification (see pages 9-11 and the Examples at pages 21-26), the inventors have first noticed that astroglia should deeply involved in the forest fire-like expansion of brain edema (see page 9) and that protection of astroglia from injury should be effective for preventing the forest fire-like expansion of brain edema (see page 10). WO '555 does not disclose those inventive concepts realized by the Inventors of the present application.

Furthermore, according to the finding of the Inventors, the protection of astroglia can be effectively performed with melatonin (see Example 1 of the present application beginning at page 19). WO '555 does not suggest this novel finding.

It is the conclusion of the inventors from the experiments of Example 1 of the present application that, without protecting astroglia from injury (including secondary injury by the forest fire-like expansion of brain edema), the brain edema could not be treated because of the specific nature of brain edema (i.e., the forest fire-like expansion). WO '555 does not suggest this novel conclusion.

Example 1 of the present application provides additional data that melatonin also protects astroglia from injury caused by a drug (page 25). This data, combined with the data on page 24 that melatonin protects astroglia from the injury caused by brain ischemia, and the data in Example 3 that melatonin reduces brain edema caused by brain ischemia, it can be concluded that melatonin can also reduces brain edema caused by a drug.

Then, *if* WO '555 suggests that melatonin could reduce brain edema caused by brain ischemia, WO '555 should also suggest that melatonin could reduce brain edema caused by a drug. However, because WO '555 does *not* correlates melatonin with brain edema, that reference fails to suggest that melatonin reduces brain edema caused by a drug. The above inconsistency is derived from the fact that the Examiner has dismissed the role of astroglia found by the Inventors in brain edema. Only by astroglia, can any brain edema resulting from a causative factor can be correlated with melatonin.

As discussed above, WO '555 discloses nothing about the relationship between the injury of astroglia and brain edema, and the protection of astroglia for treatment of brain edema. Thus, WO '555 teaches nothing about the *treatment* of brain edema.

The Examiner argues that "it would have been obvious to, one skilled in the art that a composition, which is able to prevent ischemia," while he argues also that "it should be noted in this context that WO repeatedly uses the term 'ischemic injury' 'and not just "ischemia"'.

For the inconsistency above alone, the Examiner has failed to make out a *prima facie* case of obviousness over WO '555.

In addition, the Examiner argues:

> Since ischemia is the causative factor of brain edema, it would have been obvious to one of ordinary skill in the art that a composition, which is able to prevent ischemia, would be ***preventing the edema also***. [Examiner's Answer at page 3, last paragraph.]

However, as discussed above, the claimed invention relates to a method of ***treating*** a subject actually suffering from brain edema, and not to a method of ***preventing*** brain edema. For that reason alone, the Examiner has failed to make out a prima facie case of obviousness over WO '555.

The Examiner points out that "on pages 12, line 21 through pages 13, line 12, WO '555 suggest [sic, suggests] the combination of melatonin with mannitol to reverse cerebral swelling". However, the description on page 13, lines 11-12, of WO '555 that "mannitol or its equivalent may be used to reverse cerebral swelling" simply teaches that mannitol which is a known agent capable of reversing cerebral swelling is preferably used with melatonin.

The Examiner states that "WO teaches 'ischemic injury and, one can not rule out edema as the cause of the ischemia in WO", concluding that "WO, which is suggestive of treatment of ischemic injury treatment by melatonin, is also suggestive of treatment of edema". See the Reply Brief at page 4, bottom.

Does the Examiner argue here that, because brain edema can be a causative factor of ischemia and WO '555 is suggestive of treatment of ischemic injury (caused by the ischemia)

with melatonin, WO '555 suggests that brain edema caused by the ischemia can be treated with melatonin (argument 1)?

Or, does the Examiner argue here that, because ischemic injury can be a causative factor of brain edema and WO '555 is suggestive of treatment of the ischemic injury with melatonin, WO' 555 suggests that brain edema caused by the ischemic injury can be treated with melatonin (argument 2)?

Or, does the Examiner argue here that, because WO '555 discloses treatment of ischemic injury with melatonin, treatment of brain edema which is an ischemic injury is suggested by WO '555 (argument 3)?

Appellants cannot properly reply to the Examiner's arguments since the Examiner's argument is indefinite as above. The Examiner is required do identify the basis for the obviousness rejection to enable Appellants to properly reply to the rejection.

For example, Appellants cannot make sense out of the first argument. With respect to the second argument, Appellants repeat the arguments above that treatment of ischemic injury is different from treatment of brain edema because protection of astrogria is essential in the treatment of brain edema. Additionally, the Examiner has failed to demonstrate that brain edema can be produced by the manner of WO '555 in which mannitol is introduced into 4VO models. If the third argument is applicable, the Examiner's has no sound basis for the rejection, because the Examiner has agreed with that WO '555 does not disclose treatment of brain edema as evidenced by the rejection under 35 USC §102.

Appellants submit herewith a copy of Pulsinelli et al., Neurology, 1982 Nov., 32(11), pp. 1239-1246. That reference demonstrates that no brain edema can be produced by the 4-VO method described in WO '555. At page 1243, left column, lines 8-11, the reference states that "The forebrain water content of saline-treated rats measured 24 hours after 20 minutes of 4-VO did not differ from nonischemic control animals (table 3)."

WO '555 does not disclose even that melatonin itself reduce the specific ischemic injury of WO '555, i.e., a high foot fault rate. In the Examples of WO '555, mannitol (for reversing cerebral swelling, page 13, lines 11-12) and kynurenin (for producing hypotensive effect page 13, lines 16-17) are used in combination with melatonin. Thus, WO '555 teaches at most that combined use of mannitol, kynurenin and melatonin can reduce the ischemic injury. Even when brain edema could be reduced in WO '555, the reduction of brain edema should be due to the mannitol.

In addressing Dr. Torii's Declaration, the Examiner states:

> First of all, the examiner would like to note that the declaration is not based on any experimental evidence. [Examiner's Answer at page 4, lines 4-5.]

Appellants are not aware of any rule or case law which requires that a Declaration is somehow limited to the presentation of experimental evidence. See 37 C.F.R. §1.132.

The Examiner acknowledges Dr. Torii's opinion in stating:

> while it is true that ischemia is the cause of brain ischemia, the fact that a subject has an ischemic brain injury does not mean that the subject must also have brain edema. [Examiner's Answer, page 4, lines 9-11.]

Significant by its absence is any argument or evidence in the record that Dr. Torii's statement to that effect is incorrect.

For the reasons given above and those set forth in the Appeal Brief, it is requested that the Board of Appeals and Interferences render a prompt decision reversing the Examiner's rejection.

Respectfully submitted,

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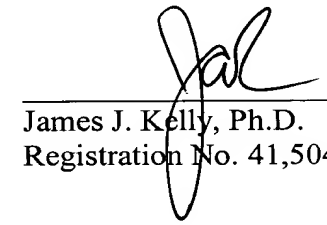

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